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AMINO-ACID DEFICIENCY PROBABLY THE PRIMARY ETIOLOGICAL FACTOR IN PELLAGRA.

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Introduction.

There is now at hand a considerable and convincing body of evidence in support of the view that diet is the primary controlling factor in the prevention and causation of pellagra. The more important part of this evidence may briefly be summarized as follows:

To begin with, account must be taken of the fact that no unequivocal evidence of the transmissibility of the disease has yet been adduced. Attempts to communicate the disease from the sick to the well by inoculation have failed in all reported instances (1, 2, 4, 5, 6). The report of a successful inoculation of a monkey by Harris (7) must be regarded, therefore, as in the highest degree doubtful; all the more as exhaustive efforts to confirm it, notably by Lavinder and Francis (8) and by Harris himself, have failed.

In harmony with the negative results of experimental inoculation are the striking freedom from danger attaching to association and contact with cases in hospitals and the singular exemption of certain groups of residents in an endemic or epidemic institutional environment. It has repeatedly been observed, first, that at institutions (whether special or general hospitals) receiving cases of pellagra for treatment, physicians, nurses, attendants, etc., in frequent contact with the disease and directly or indirectly with the body discharges of persons sick with it, practically never develop the disease while so employed (9, 10, 11, 12); second, that employees (nurses, attendants, etc.) resident in institutions in which the disease has long been endemic or at times epidemic, many of whom also come in frequent association or intimate contact with cases of the disease or their body discharges or both, practically never contract it while so employed and so resident (11, 13).[1]

The striking exemption of certain groups residing in an endemic institutional environment has been found, in the instances studied by us, to be consistently associated with a significant difference in diet.

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[1] In an interesting account of medico-military observations in Rumania during the war, Külz (Arch. f. Schiffs u. Trop. Hyg. 1918, vol. 22, pp. 401-403), a German Army surgeon with the army of occupation, remarks that "the fact that the several hundred thousand of the military personnel, in spite of the closest contact with the Rumanian population (among whom pellagra was prevalent), remained free from the disease, is evidence of very great weight in support of the argument against infection." Of similar import seem to be the conclusions of a recent Italian pellagra commission [Lustig and Franchetti: Lo Spermientale, 1921], as may be seen by the following taken from a review of this commission's report by J. Rosslyn Earp (Trop. Dis. Bull. 1921, vol. 18, p. 226): "During the period of hostilities when many infectious diseases, especially tuberculosis and malaria, showed a marked rise in morbidity, pellagra, on the other hand, diminished. They consider this important evidence in support of the theory that pellagra is a deficiency disease. This theory obtains further credit from the fact that during the war the diet of the rural populations was both richer and more varied than it had been formerly. The idea that an infection may be carried in certain foods is further discredited in that war conditions resulted in an unusual amount of transport of foodstuffs."

The controlling importance of diet is shown by the part it plays in the treatment, prevention, and production of the disease. Active cases of pellagra respond promptly and strikingly to an exclusively dietary treatment (14, 23). The relatively rare exceptions are no more than might be anticipated when the experience in scurvy and beriberi are kept in mind. The natural tendency to recovery without change of environment, and seemingly without therapeutic interference, is associated with a seasonal change in diet (15).

Of outstanding significance are, on the one hand, the demonstration that pellagra may be completely prevented by means of a suitable diet, without intervention of any other known factor, hygienic or sanitary (16, 17, 18, 19), and, on the other, the absence of any sound evidence that the disease is preventable by any other means (20, 21).

Although, as has already been stated, all attempts to transmit the disease from the sick to the well by inoculation have failed, an experiment to induce the disease in the human subject by feeding, carried out by Goldberger and Wheeler (21, 22) in 1915, was completely successful. At least 6 of 11 convicts who volunteered for the experiment and who subsisted on a diet consisting principally of the cereals, wheat, maize, and rice, with pork fat and some fresh vegetables (sweet potatoes, turnips, cabbage, greens), developed evidence which experienced observers recognized as that of pellagra; whereas, of a large number of controls, none presented any evidence justifying even a suspicion of the disease. In this connection it may be noted that symptoms and pathological changes resembling more or less markedly, but not certainly identical with, those occurring in pellagra have been reported in animals experimentally fed certain faulty diets (23, 24, 25, 26).

Finally, reference should perhaps also be made to the idea that in the causation of the disease there is, besides diet, also an essential infective factor. According to this a faulty diet operates merely by lowering resistance to infection. This view has elsewhere already been discussed by Goldberger and Wheeler (21), who have shown that it is untenable except in the form that a poor nutrition of a specific kind, the result of a faulty diet, is essential to enable the hypothetical infection to establish itself; that is, in the form calling for the concurrence of two specific extrinsic factors.

With respect to this more restricted conception it may be said, first, that it implicitly recognizes diet as the primary controlling factor; second, that unequivocal evidence of the existence of an essential infective factor has not yet been adduced; and, finally, that all the well-ascertained phenomena of the disease are either explicable by or at least not inconsistent with an exclusively dietary etiology, thus rendering superfluous the assumption of a second essential factor.

While it thus is clear that in the prevention and causation of pellagra, diet plays the dominating rôle, the question of the essential dietary factor or factors concerned is still undetermined.

In this paper we desire to record certain observations which bear directly on this question. First, however, we shall pass in review the literature more or less closely related thereto.

Review of Literature.

A review of the older literature which, in the main, concerned itself with maize, particularly spoiled maize, although very interesting in retrospect, does not seem sufficiently pertinent in the present connection to warrant full presentation. It will suffice to recall the theory elaborated by Lussana and Frua and the closely related view advocated by Calmarza. Lussana and Frua (24) contended that pellagra is due to an "insufficient neuromuscular repair" arising from "an alimentation of proteinaceous insufficiency in comparison with nondeficient respiratory quota" in a diet "fundamentally and almost exclusively composed of maize." This theory of relative protein insufficiency in pellagra may almost be considered the prototype of the theory advanced over a score of years later by Takaki[1] (28) in connection with beriberi and a rice diet.

Among other evidence adduced by Lussana and Frua in support of their contention was the markedly more favorable result of dietetic ("restorative nutritive") treatment based on their own theory than that obtained by treatment based on other hypotheses.

In this connection reference may be made to the fundamentally rather closely related theory suggested a few years ago by Deeks (29). Deeks seems to group pellagra with "hyperchlorhydria," "flatulent dyspepsias," "acute rheumatism and rheumatic affections," and "nephritis," as a "carbohydrate diathesis." He believes that it is not corn alone "but any cereal or starch food in conjunction with cane sugar, in a warm climate where there is lessened metabolic activity and consequent inadequate elaboration of digestive elements which initiates the autointoxication responsible for the symptom-complex known as pellagra." "The proof thereof," he goes on to say, "lies not in the determination of the elusive complex physicochemical substances, the result of fermentation or defective metabolic elaboration, but in the results obtained by physiological treatment based on the above-mentioned hypothesis." His treatment consists "(1) in limiting the nourishment absolutely to fresh fruit juice, preferably orange, meat broths, and milk, as long as there is nausea or vomiting, and the absolute avoidance of everything which contains sweet or starchy elements; (2) in the administration of from 15 to 30 drops of dilute nitric acid in three-fourths of a tumbler of water three times daily on an empty stomach. I have found by practical experience" he states, "that no substance will relieve as quickly or as satisfactorily gastric acidity as this mineral acid. When the stomach condition improves, which is generally in three or four days, a carbohydrate-free diet is ordered. This consists, in addition to the above, of eggs, meats of all kinds, fish, green vegetables, such as lettuce, celery, onions, tomatoes, beets, carrots, spinach, chayoti, vegetable marrow, okra, green peas, string beans, egg plant, etc., and fresh fruits of all kinds, there being no limitation." It may here be remarked, as has already been pointed out by Goldberger, Wheeler, and Sydenstricker (44), that the idea that the production of pellagra is dependent on the excessive consumption of carbohydrates was suggested at least as far back as 1796 by Albera and by Strambio (69). The essentials of Deeks's treatment are those of a long line of his predecessors, beginning with Casal himself.

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[1] Takaki stated his theory as follows: "The various investigations made during the past four years lead me to the conclusion, finding no other possible cause, that a wide departure of nitrogen and carbon from the standard proportion (1 to 15) essential to the maintenance of health, resulting from a great deficiency of nitrogenous substances and a great excess of carbohydrates in food, is the cause of kak'ke [b eriberi]."

Calmarza (4) like many (if not most) Spanish students of the disease denied that maize had any necessary connection with pellagra and vigorously contended that the disease was due solely to an alimentation deficient in animal food, a diet too largely vegetable, providing, he claimed, too little nitrogen for human needs. Calmarza's contention did not receive the attention which it merited largely because of Costallat and Roussel (3), who, being enthusiastic zeists, cast doubt upon the diagnosis of the cases of pellagra without maize reported by Calmarza and other Spanish observers.

The views relating to the nature of the dietary defect that may be considered as immediately pertinent to the present discussion date from 1912. In that year Funk (30) included pellagra provisionally in a group of "deficiency diseases," all of which, he stated, could be prevented and cured by the addition of certain preventive substances called by him "vitamines."

Inspired by Funk's work and the other, then recent, developments in beriberi, Sandwith (31) suggested that pellagra might be a "deficiency disease, waiting for a 'vitamin' to be discovered." At the the same time, having in mind the work of Wilcock and Hopkins with zein, he vaguely suggested the possibility of a tryptophan deficiency on the basis, it would seem, of the mistaken impression that zein was the sole protein of maize, and in the belief that inferior or damaged maize was the cause of pellagra.

In 1914 Nightingale (32) from his experience with a disease which he called "zeism," but which must be regarded as pellagra, concluded that the disease was due to the loss of some essential nutritive constituent during the process of grinding maize into meal, "probably of the nature of an organic salt." This recalls the suggestion made by Petrof (50) in 1907 that pellagra is due to a deficiency in phosphorous. Petrof attempted to show that this deficiency arose as the result of a maize diet, of which the maize was poor in phosphorus, its poverty in phorphorus arising from being cultivated in a lime-poor soil.

In 1914, also, there was suggested by Voegtlin (33) that in the study of the etiology of pellagra, serious consideration would have to be given to "(1) a deficiency or absence of certain vitamines in the diet; (2) the toxic effect of some substances, as aluminum, which occur in certain vegetable food; (3) a deficiency of the diet in certain amino-acids." Later, in a study of the influence of vitamines on the clinical course of pellagra, Voegtlin, in association with Neil and Hunter (34), reported that the administration of extracts from yeast and rice polishings, which were highly efficient for the prevention of avian polyneuritis, in general failed to modify the course of the disease, but the administration to pellagrins of protein-free extracts obtained from liver and thymus gland presumed to contain both the antineuritic substance and the fat soluble vitamine "was followed by an improvement in their condition apparently comparable to that produced by the consumption of a diet rich in fresh animal proteins." The conclusion drawn was that "the dietary defect responsible for pellagra is distinctly (qualitatively) different from and perhaps more complex than the one causing fowl polyneuritis and human beriberi."

McCollum, Simmonds, and Parsons, as a result of studies of faulty diets in rats (35) expressed the belief that pellagra is primarily associated with the unsatisfactory character of three dietary factors, namely, fat-soluble A, mineral elements, and protein mixture. A year later these workers, after having attempted to produce in rats a condition analogous to pellagra in man by feeding their animals with diets similar to the diet employed by Goldberger and Wheeler in their experiment on convicts, and observing in them only a "generalized poor condition," concluded that pellagra is caused by an infectious agent (36). It may be remarked that this conclusion appears in large measure to be based on the unwarranted assumption that the distinctive symptoms observed in man, resulting from feeding a given diet, must necessarily be exactly reproduced in another species, in this case the rat.

As a result of his experience with pellagra among Armenian refugees, White (17) has suggested that the causal factor may be a deficiency of vitamine or of some other essential components of the diet, such as tryptophane or an insufficiency or unsuitability of one of the proximate principles in the dietary, such as the protein or fat.

On White's invitation, Wilson (37) examined the diet concerned in the outbreak among these refugees and as a result expressed the opinion that the most probable cause of the outbreak was, first of all, the low biological value of protein, next, the low total energy value, and, finally, the low fat value. Wilson gave the results of his further studies to the committee of enquiry which investigated the outbreak of pellagra among Turkish prisoners of war. This committee (38) concluded that pellagra is due to deficiency in protein, as guaged by its biological value.

Recently a full report of Wilson's important studies have appeared (39). In this he makes comparisons of diets known to have been connected with pellagra with those of known value in curing and preventing the disease, from which he concludes that the etiological factor is a deficiency of protein in the food, best determined by an estimation of its biological value by means of Thomas's figures. He argues against a deficiency in vitamines, citing a markedly favorable effect in the reduction of pellagra observed among the inmates of the Abassia Asylum for the Insane at Cairo, following the addition of 45 grams of meat and 50 of milk to a diet which already containing 100 grams of meat, 50 grams of milk, and 300 grams of fresh vegetables, it was difficult for him "to suppose was lacking in either vitamines, using the term generally, or in salts of lime, or that the additions made could have added anything of great importance in these respects." The deficiency of protein may, he considers, be "(*a*) primary, in which the supply is insufficient for the individual requirement or, when, owing to the indigestible character of the food, a somewhat restricted supply can not be utilized to the normal extent; (*b*) secondary, in which, owing to digestive disturbances or other causes, the supply of protein can not be assimilated." He looks upon indicanuria as an important indication of the loss of protein in the intestine, the amount present being, he estimates, sometimes sufficient to account for the loss to the body of a large proportion of the protein intake. He considers the indicanuria as closely related to the deficiency of gastric hydrochloric acid. Labor, by raising the level of protein requirement, especially when there is a deficient energy supply, is considered a factor in the causation of pellagra. He suggests that a deficiency of cholestrol may be related to some of the symptoms.

Wood (40) from some experiments with fowls, and by reason of seemingly favorable results of treatment with maize germ and wheat bran, is disposed to suspect that a vitamine-B deficiency is involved in pellagra. However, he points out that there may be something else in the maize germ and the cortex of wheat that may account for the results observed. It may be remarked that there is nothing to show that other changes in the diet made at the same time could not explain the favorable results Wood attributes to maize germ and wheat bran.

In April, 1920, Chick and Hume (25) reported symptoms resembling those of pellagra, produced in three monkeys by prolonged feeding on a low protein diet in which the proteins, almost exclusively those of maize, were at the same time of low biological value. Whether the condition of malnutrition produced in these animals may properly be regarded as corresponding to that of pellagra in man, depends, in the present state of our knowledge, on whether the eruption observed in one of the animals actually corresponded to the dermatitis of pellagra in man. So far as may be judged by the published description and colored drawing of the eruption, this is very doubtful. That some of the symptoms observed in these monkeys may have been due to an amino-acid deficiency in the experimental diet seems not improbable, and the improvement reported as having been observed in two of the three animals treated with tryptophane would suggest that a deficiency in at least this one amino-acid was involved in the cause of the malnutrition observed in these animals.

McCarrison (26) has called attention to the parallelism of symptoms and pathological lesions of pellagra with those in the animals (monkeys) experimentally fed by him on vitamine-deficient diets. On the basis of these analogies he considers it probable "that deficiency of vitamines and the consequent disturbance of digestive and endocrine functions play an important part in the production of pellagra." Certain other considerations lead him to believe "that pellagra may result either from deficient protein supply or from deficient protein assimilation consequent on vitamine insufficiency or from a combination of both these causes." McCarrison does not seem to have actually worked with the disease himself.

According to Hess (41) "the experiences in the Central Empires during the war render it improbable that pellagra is due merely to a lack of adequate protein. Adequate protein was lacking to a marked degree—milk, cheese, eggs, meat were all unavailable. Nevertheless there was no prevalence of pellagra throughout these years." Evidently Hess assumes that the protein of milk, cheese, eggs, and meat alone is "adequate" protein.

Impressed by certain striking epidemiological features and the negative results of animal inoculation experiments, Goldberger (42) suggested in 1914 that pellagra is a disease essentially of dietary origin caused either by a deficiency in the diet of some essential element or by the presence of some element in excessive amounts; that is, by a diet faulty in some undetermined respect, but the fault in which could be corrected by an increase in the fresh animal food component (13, 14).

In 1918 Goldberger, Wheeler, and Sydenstricker (43) reported that the indications afforded by a study of the diet of nonpellagrous and of pellagrous households clearly suggested that the pellagra-producing dietary fault is the result of some one or, more probably, of a combination of two or more, of the following factors: (1) A physiologically defective protein supply; (2) a low or inadequate supply of fat-soluble vitamine; (3) a low or inadequate supply of water-soluble vitamine; and (4) a defective mineral supply.

In harmony with these indications are those afforded by the result of Goldberger and Wheeler's (21) feeding experiment in convicts. The experimental diet, they state, was probably faulty in some degree with respect to the protein, mineral element, antineuritic, and, possibly also, with respect to the fat-soluble vitamine. From this they inferred that in relation to the production of pellagra their study suggested that the dietary factors to be considered as possibly essential are an amino-acid deficiency, a deficient or faulty constitution of the mineral element, possibly, but doubtfully, a deficiency in the fat-soluble vitamine, and perhaps some as yet unknown factor.

In a more detailed report of the study of the diet of nonpellagrous and of pellagrous households, Goldberger, Wheeler, and Sydenstricker (44) conclude that the indications of their study suggest that "the pellagra-producing dietary fault is the result of some one or of a combination or combinations of two or more of the following factors: (1) A physiologically defective protein (amino-acid) supply; (2) a defective or inadequate mineral supply; (3) a deficiency in an as yet unknown dietary essential (vitamine?)," none of the known vitamines being regarded as necessary factors.

Present Study of Preventive Dietary Factors.

The following gives the details of some observations which were made in the course of studies of the prevention of pellagra at the Georgia State Sanitarium, one of the large southern asylums for the insane. We are deeply grateful to the trustees and officers of this institution for their sustained interest and cooperation.

I. *Mineral supplement.*—The high value which our experience at this asylum and the other Service investigations had taught us to attach to milk, both as a prophylactic and therapeutic agent, suggested, among other things, the possibility that its value might be due to the inorganic elements of its ash. We therefore arranged to supplement the institution diet of a group of colored and one of white patients with an inorganic salt mixture, each daily dose of which contained the inorganic elements of the ash in a liter of whole milk (45), this quantity of fresh whole milk as a supplement to the institution diet having shown itself to have decidedly beneficial effects in both prevention and treatment. We began with a single mixture of the following composition (quantities for one individual per day) prepared for us by Dr. Atherton Seidell, of the division of chemistry of the Hygienic Laboratory:

	Grams.
$CaH\,PO_4 2H_2O$	5.15
Na_2SO_4	1.51
$Mg\,Cl_2$	0.47
KCl	1.49
$K_3C_6H_5O_7H_2O$	1.79
Iron and ammonium citrate (17 per cent Fe)	.07

Having experienced some administrative difficulties in its use on a large scale, it was replaced at the end of about one month by two mixtures which were suggested and prepared for us by Dr. Elias Elvove, of the division of chemistry of the Hygienic Laboratory. Together these furnished, qualitatively and quantitatively, the same inorganic elements as had the first mixture, but each could be separately dissolved in water and thus conveniently mixed with the food.

The composition of each of these is as follows (for one individual per day):

Mixture A

	Grams.
$Ca(C_2H_3O_2)_2\,H_2O$	4.187
$CaCl_2$	0.685
$Mg\,Cl_2$	0.470
KCl	0.495
$NaCl$	0.054
$FeCl_3$	0.007

Mixture B.

$Na_2\,SO_4$	1.510
KH_2PO_4	4.079

Mixture B, in aqueous solution, was stirred up with the breakfast cereal and hash and A with the food at the mid-day meal. In order to make sure of a liberal supply of iodine, we began, at about the time the change to the two mixtures (A and B) was made, the daily addition to the evening meal of two drops of the sirup of the iodid of iron (U. S. P.). Incidentally, this increased somewhat the allowance of iron, an element in which the ash of milk is poor.

The amount of each of the nine mineral elements believed to be essential in mammalian nutrition which these daily supplements yielded is shown in the following table, which has been prepared to permit also of a comparison with the elements yielded by the salt mixtures extensively used in their studies by Osborne and Mendel (46) and by McCollum (47) and associates, respectively.

TABLE I.—*Number of grams of the specified elements yielded by the daily supplement of minerals and a comparison with quantities which would be yielded by salt mixtures extensively used by Osborne and Mendel and by McCollum, respectively, if supplied to yield the same amount of Ca.*

	Ca.	Mg.	K.	Na.	P.	Cl.	S.	Fe.	I.
Mixtures A and B, with 2 drops of sirup of iodid of iron (U. S. P.)	1.20	0.12	1.43	0.51	0.93	1.06	0.34	0.0034	0.005
Mixture of Osborne and Mendel	1.20	.16	.87	.30	.72	1.12	.07	.023	[a].0003
Mixture No. 185, of McCollum	1.20	.24	1.88	.55	1.66	.46	.31	.83	[b]Trace.

[a] Besides the elements shown in the table, this mixture includes traces of fluorine and aluminum.
[b] Supplied in the drinking water.

It will be noted that while there are some differences among these three mixtures, there is a quite marked general similarity in the quantity of the elements yielded. On the basis of an identical yield of calcium the quantity of K, Na, P, and Cl supplied by our minerals is seen to be intermediate between that furnished by the mixture of Osborne and Mendel on the one hand and that of McCollum on the other. Our supplements differed perhaps most markedly from either of the other mixtures in the much lower yield by ours of iron.

At this juncture it may be noted that the bulk of the institution diet—the diet of the inmates whose attacks of pellagra we are about to consider—consisted of the cereals maize, wheat, and rice, some dried legumes, and a little beef. The mineral element supplied by such diet is, according to McCollum (48), too low in the elements sodium, chlorine, and calcium.

Recalling that in the preparation of the various dishes constituting the diet, table salt is always freely used, there could here, therefore, quite independently of the mineral supplements, at no time be a question of an inadequate supply of the elements sodium and chlorine. According to Sherman (45) the standard allowance of calcium in a man of 70 kilograms, with an energy requirement of 3,000 calories, should be 0.69 gram. Accepting this, it follows that our mineral supplement afforded a very liberal supply of this element, and there can thus be no question of a calcium deficiency in the diet so supplemented even when this was not entirely consumed.

In spite of the undoubted improvement in the institution diet thus brought about, a number of cases of pellagra occurred in individuals consuming it. Following is a brief summary of the significant points in the history of five cases in individuals known to have consumed during considerable periods practically their entire allowance of minerals.

Case 1. C–O: White female, age 32, weight 44.5 kilograms, had pellagra in 1913, 1914, and again in October, 1920. Began taking the mineral supplement on December 10, at which time she presented no recognizable symptoms of pellagra. The sirup of the iodid of iron was begun on January 25. On the following June 7 this patient developed a pellagrous dermatitis, notwithstanding that during this period of at least 4½ months she consumed practically 100 per cent of the minerals furnished.

Case 2. H–L. L: White female, age 44, weight 35.8 kilograms, had pellagra 1912, 1914, and 1918. Began taking the mineral supplement December 10, and the sirup of the iodid of iron on January 25. On the following June 17 this patient developed the distinctive dermatitis, although it is estimated that she consumed during the interval fully 95 per cent of the minerals furnished.

Case 3. K–S: White female, age 54, weight 62.5 kilograms, had pellagra 1915, 1918, and again in September, 1920. Began taking the mineral supplement on December 10, at which time she was free from recognizable symptoms of pellagra. Administration of the sirup of the iodid of iron was begun January 25. On May 4 she developed the dermatitis of pellagra, although her record of food consumption during the interval indicated an intake of fully 95 per cent of the minerals furnished.

Case 4. S–E: Colored female, age 55, weight 39.2 kilograms, had pellagra in 1915, 1918, and again in August, 1920. Began taking the mineral supplement on December 16, by which time she was free of recognizable symptoms of pellagra. The sirup of the iodid of iron was begun on January 26. On the following May 30 she developed the dermatitis of pellagra, although she is recorded as having taken during the interval fully 95 per cent of the minerals.

Case 5. W–M: Colored female, age 55, weight 41 kilograms, had pellagra in 1917, 1918, 1919, in April, and a second dermal attack early in November, 1920. Like "S–E" she began taking the mineral supplement on December 16, by which time recognizable symptoms of pellagra had disappeared. The sirup of the iodid of iron was begun on January 26. On April 4 this patient developed the dermatitis of pellagra, although in the interval she consumed, we estimate, fully 95 per cent of the minerals furnished.

II. *Vitamines with supplement of minerals.*—Although, as will presently be indicated, there is reason to believe that the institution diet includes, in general, sufficient of the vitamine-containing foods to provide at least the minimum requirement of the known vitamines, the supply of these, particularly of vitamines C and A, is quite irregular and fluctuates widely, depending as it here does practically exclusively on the supply of fresh vegetables, a supply that is markedly influenced by season and other factors affecting availability. The supply of vitamine B fluctuates less and is more regular than that of C and A, since such sources of this vitamine as unbolted maize (51) meal in form of corn bread is daily, and legumes (52) (lima beans, navy beans, or cowpeas) are frequently (though irregularly) served at the midday meal. Accordingly, with the object of further improving the diet by correcting the possible faults arising from these causes, we replaced, on and after May 24, the fluctuating and irregular supply of fresh vegetables in the diet of those receiving the supplement of minerals, with a regular daily supply of 3 ounces of the juice expressed from canned tomatoes, and one-half ounce of cod-liver oil, and, on June 19, the variable and irregular supply of legumes with a regular daily ration of at least one-half ounce of cowpeas.

In this connection it may be observed that canned tomato juice has been shown to be an excellent antiscorbutic (53, 54, 55, 56). In comparison with lemon and orange juice, its antiscorbutic power would seem to be somewhat inferior. According to Hess, 4 c. c. daily of strained canned tomato juice are sufficient to protect the guinea pig, whereas of either orange or lemon juice only about 3 c. c. daily are required (57)—a ratio of about 4 to 3.

Recalling that the experience of the British Navy and of Arctic expeditions has amply demonstrated that not over 1 ounce of lemon juice fully protects the sailor and the Arctic explorer against scurvy (58, 59), it would follow, on the basis of this ratio, that about 1⅓ ounces of canned tomato juice should serve the same purpose. Our allowance of 3 ounces daily for these small, inactive inmates would therefore seem to be a very liberal one.

Tomato juice has also been found to be quite rich in the water-soluble and the fat-soluble vitamine. Its antineuritic potency is indicated by the fact that Hess and Unger (55) have found that pigeons suffering from polyneuritis could be cured by giving them 5 c. c. of this foodstuff daily. Presumably a smaller quantity would suffice to prevent the development of the polyneuritis in this highly susceptible animal. As a source of fat-soluble vitamine, tomato juice is far inferior to cod-liver oil.

This oil, of all foods so far studied, would seem to be the richest in vitamine A. Some samples quantitatively tested have been found 250 times as potent as butter (60, 61). Allowing for variations in potency of different samples and assuming that the sample used by us had only 10 per cent of this value, the daily administration of half an ounce of the oil would, on this extremely conservative basis, be equivalent to a daily consumption of the vitamine in some 12 ounces of butter. So far as can be judged, this quantity of butter would supply more than enough vitamine A for any human need. It would appear reasonably certain, therefore, that our cod-liver oil supplement alone furnished a more than ample quota of this food essential.

Besides its exceptional richness in the anti-xerophthalmic essential, cod-liver oil, it may be noted, seems also to carry an abundance of an as yet not fully defined antirachitic factor (62, 63).

Notwithstanding these advantageous additions and modifications, three cases of pellagra developed in individuals known to have taken all of the cod-liver oil and tomato juice and to have consumed practically all of the cowpeas and minerals furnished. The following is a summary of the significant points in the history of these cases.

Case 6. J–F: Colored female, age 45, weight 54 kilograms; had pellagra in 1914 and again in April, 1920. Began taking the mineral supplement December 14, 1920, at which time she was free of active symptoms of pellagra. Beginning January 26, she was given 2 drops of the sirup of the iodid of iron daily. On May 24, began taking cod-liver oil (one-half ounce) and canned tomato juice (3 ounces) daily. Between June 3 and August 13 consumed daily, among other things, an average of approximately 1 ounce of dry cowpeas (boiled) and about 2 ounces of unbolted maize meal (as corn bread). After August 13 the daily consumption of cowpeas averaged approximately one-half ounce and of whole maize meal 3½–4 ounces. Throughout she took practically all of the mineral addition. Notwithstanding all this, however, this patient developed the beginning of a pellagrous dermatitis on August 24.

Case 7. S–M. L: Colored female, age 37, weight 43.6 kilograms. Had pellagra in October, 1920. Began taking the mineral supplement on December 14, at which time she was free from active symptoms of pellagra. On January 26 she began receiving 2 drops of the sirup of iodid of iron daily. On May 24 began taking cod-liver oil (one-half ounce) and tomato juice (3 ounces) daily. Between June 3 and August 13 consumed daily, among other things, an average of approximately 1 ounce of dry cowpeas (boiled) and about 2 ounces of unbolted maize meal (as corn bread). After August 13 the daily consumption of cowpeas averaged approximately one-half ounce and of maize meal approximately 3½–4 ounces. Throughout she consumed practically all the mineral supplements. In spite of all this, however, this patient developed a mild but classical pellagrous dermatitis on September 16, 1921.

Case 8. T–E: Colored female; age 28, weight 40.2 kilograms. Had pellagra in October, 1916, and again in June, 1920. On December 14, at which time she was free of active symptoms of pellagra, began taking the mineral supplement. On January 26 she began receiving 2 drops of the sirup of iodid of iron daily with her supper. On May 24 she began taking cod-liver oil (one-half ounce) and tomato juice (3 ounces) daily. Between June 3 and August 13 she consumed daily, among other things, an average of approximately 1 ounce of dry cowpeas and 1½–2 ounces of unbolted maize meal (as corn bread). After August 13 the daily consumption of cowpeas averaged approximately one-half ounce and of maize meal 3½–4 ounces.

On September 19 this patient developed the beginning of a pellagrous dermatitis in spite of having consumed practically all of the minerals and vitamines furnished during a period of at least four months.

In addition to the foregoing we observed two cases in individuals who, because of capricious appetities, had not so regularly consumed the entire mineral supplement nor quite all the cowpeas, but who, by reason of the separate administration of the tomato juice and cod-liver oil, were known to have consumed all of their allowance of these foodstuffs. The significant points in the histories of these two cases are as follows.

Case 9. P–A: Colored female, age 45, weight 40.2 kilograms. Had pellagra in 1917, 1918, and 1919, and October, 1920. She was free from active symptoms of pellagra on December 14, 1920, when she began taking the mineral supplement. On January 26 she began receiving 2 drops of the sirup of iodid of iron daily. On May 24 began taking and thereafter took regularly fully one-half ounce of cod-liver oil and 3 ounces of tomato juice daily. Between June 3 and August 13 she consumed regularly as part of her diet practically all of a daily allowance of fully 1 ounce of cowpeas and of approximately 2 ounces of unbolted maize meal (as corn bread). Between August 13 and October 9 the consumption of cowpeas was reduced to a little under one-half ounce (approximately 10 or 11 grams) daily, but that of maize meal was increased to between 3 and 4 ounces a day.

During the period June 3 to October 9, 1921, the daily consumption of the mineral supplement was not complete, but is estimated to have equaled fully 80 per cent of that offered.

So far as can be judged, the shifts in food consumption noted would hardly seem to have effected any change in the quantity of vitamine B intake, the reduced consumption of cowpeas being probably fully compensated for by the increased consumption of maize meal. The reduced mineral intake would still, we should judge, furnish plenty of the elements sodium, chlorine, and calcium. In spite of all this, however, a pellagrous dermatitis made its appearance about October 10, 1921.

Case 10. N–M: Colored female, age 41, weight 41 kilograms. So far as known had her first attack of pellagra in July, 1920. She was free from active symptoms of pellagra on December 14, when she began taking the mineral supplement. Like Case 9, on January 26, she began receiving two drops of the sirup of the iodid of iron, and on May 24, one-half ounce of cod-liver oil and 3 ounces of tomato juice daily.

Between June 3 and August 13 she consumed daily as part of her diet an average of a little short of 1 ounce of cowpeas (about 25 grams) and upward of 1½ ounces of unbolted maize meal (as corn bread). After August 13 and up to September 20 the consumption of cowpeas was reduced to a daily average of slightly under one-half ounce (about 12 grams), but that of maize meal was increased to a daily average of between 3 and 4 ounces.

Between June 3 and September 20 her food consumption was such that her intake of calcium is estimated to have been fully 90 per cent of that offered.

It would appear that in this as in Case 9, the variation in appetite did not materially affect the intake of vitamine B and, since the cod-liver oil and tomato juice were regularly administered apart from the other food and always completely ingested, the intake of the other vitamines was not at all affected. With respect to the mineral elements of special interest (calcium, sodium, and chlorine), the slight reduction of intake, considering the liberal supply may, we judge, be regarded as negligible. Notwithstanding all this, however, a classical pellagrous dermatitis began its development on September 22.

SIGNIFICANCE OF OBSERVATIONS IN PRESENT STUDY.

It will doubtless have been noted that in all the cases cited the individuals attacked had had one or more previous attacks of the disease. This was not an accidental circumstance. In selecting individuals for observation and study, we purposely chose those who had had previous attacks, in the belief that in a group so chosen there would be a greater chance of the development of cases than in a group of individuals not previously attacked, and therefore the failure of such development would be all the more significant of the value of the preventive measures being tested. For, although a pellagra recurrence must be regarded as etiologically fundamentally identical with an initial attack (14), there are nevertheless certain intrinsic factors which, exposure being equal, may conceivably operate to make more probable that a pellagrin will suffer a recurrence than that a non-pellagrin will develop an initial attack. Of these factors, three may be cited in the present connection.

There is, first of all, the possibility that some of those who have suffered an attack of the disease have not, by reason perhaps of inadequate treatment, fully recovered their normal nutritional status. For such, it may be assumed that the minimum supply of essential food factors must be greater than for the average normal individual since, conceivably, there is not only the need for taking care of current requirements, but also for the repair or correction of residual morbid processes or changes and, perhaps, also to satisfy a residual shortage of some essential nutritional elements.

There is next the probability that some, if not all, such individuals have suffered some (possibly permanent) damage to the digestive organs and glands which may conceivably lead to a lowering of efficiency or to an unfavorable modification of the digestive processes and thus to an inferior utilization of some of the ingested nutrients. It is known, in fact, that gastric anacidity is a frequent sequel of the disease and this, as both Murlin (64) and Wilson (39) suggest, probably explains the tendency in convalescents for intestinal putrefaction to take place high up in the intestines (65, 66) with the production of waste products, manifested by the appearance of an excess of hippuric acid and of indican in the urine. While this disturbed digestion may, as Wilson further points out, lead to serious loss of protein and, possibly of a little fat, it should perhaps be observed that it is not known that any other food factors are materially affected nor that the processes of absorption are appreciably interfered with.

Finally we have the possibility if not the probability that the pellagrin may be an individual whose minimum physiological requirements are normally somewhat above the average.

The circumstance, therefore, that our observations were in individuals with histories of one or several previous attacks and thus probably with requirements for a supply of nutrient factors in some measure above the normal average, makes it more than ordinarily important that in evaluating the significance of these observations due consideration be given to the question of the adequacy of supply of the dietary factors the rôle of which in pellagra prevention we are seeking to determine.

Mineral supplement.—It has already been pointed out that by reason of the nature of the shortcomings, with respect to the mineral element, of the type of diet provided the asylum inmates, the mineral supplement furnished by us coupled with the table salt used in the preparation of the several dishes, would, with reasonable certainty, not only correct such possible shortcomings but also provide a large margin of safety. So far as existing knowledge permits one to judge, both the total quantity and the composition of the mineral consumed may properly be regarded as having been fully adequate for the needs of the individuals concerned. Therefore the failure of our mineral addition to prevent the occurrence of the disease in the cases cited would seem quite clearly to indicate that a mineral deficiency is not an essential factor in the production of the disease. This interpretation is materially strengthened by the fact that lean meat, known to be poor in ash, is a valuable preventive of the disease. Indeed our experience leads us to believe that on the basis of protein, fresh lean beef is, gram for gram, at least as efficient a prophylactic as is milk, a food exceptionally rich in minerals.

Vitamines with minerals.—The failure of our attempt to prevent pellagra by supplementing the institution diet with mineral elements which, it seems safe to assume, made good the shortcomings of the ash constituents of the diet, is significant, however, not only in relation to the mineral factor itself but also as relates to a combination of this with the known vitamines.

In the large section of the asylum (colored females) under our observation, we have found symptoms of scurvy and of beriberi of such very exceptional occurrence as to leave no room for doubt that the institution diet provides at least the minimum requirement of the essential antiscorbutic and antineuritic vitamines. Similarly, although inflammatory conditions of the eye occur from time to time among the asylum inmates, we have at no time observed among them any condition which did not respond quite readily to mild local antisepsis, a response which, it is believed, would not have occurred in cases of ophthalmia the result of a vitamine-A deficiency. Therefore, if this form of ophthalmia has occurred among the inmates under our observation such cases must, we feel, have been both rare and very mild, for, although on the alert, we have recognized none. This suggests that the asylum diet contains, in general, sufficient vitamine-A to prevent the development of this specific eye disease.

In the light of these considerations it would seem to follow that cases 1–5, above cited, developed in spite, not only of what, we believe, may properly be regarded as a liberal mineral intake (supplement of minerals plus minerals in institution diet), but also in spite of an intake at the same time of each of the three known vitamines included in the institution diet, an intake which, if not liberal, would seem, in general, to be at least adequate to prevent recognizable symptoms of a specific deficiency.

Recalling what has already been said of the richness in vitamines A, B, and C of canned tomato juice, and in vitamine A and the antirachitic factor of cod liver oil, and taking into account also the fact that both dry cowpeas and unbolted maize meal are good sources of vitamine B (51, 52), it would seem that the modifications of the institution diet, already referred to, as the result of which these vitamine-bearing foods were regularly included in the daily ration, very greatly improved it in all these respects. If, as we believe, the institution diet, in general, supplies at least the minimum needs of each of the three known vitamines, the diet modified and supplemented, as described, may reasonably, we believe, be regarded as supplying them in fully adequate quantities even for individuals of the type with which we were dealing.

Therefore the development of recurrences in five individuals (cases No. 6, 7, 8, 9, and 10), each of whom had, as already detailed, consumed daily for periods of at least two and one-half months before the appearance of the eruption not only what we believe to have been an adequate mineral supplement but also what we judge to have been an abundance of all known vitamines, would seem to indicate that a deficiency of these dietary factors, individually and collectively, is not essential in the causation of the disease.

The development during the past few years in our knowledge of nutrition seems to warrant the belief that besides an adequate energy supply the following dietary factors are essential for normal physiological well being: An adequate quota of protein of good biological quality; a suitable mineral supply; a sufficient supply of vitamines, A, B, and C, and, possibly, of an as yet not definitely identified antirachitic factor.

With regard to energy supply we estimate that the food actually consumed yielded an average of approximately 1,800 calories [1] daily. Considering the mild climate, the small size and inactive habit of the patients concerned, this should have fully supplied their energy needs. The cases of pellagra under consideration would seem to have occurred therefore in spite not only of a liberal intake of essential minerals and vitamines but also of an adequate energy supply.

Thus, by a process of exclusion we are led to conclude that of the known dietary essentials the protein factor alone was concerned in our failure to prevent the development of the cases herein cited. And if our interpretations are, as we believe, sound (and if all dietary factors essential in human nutrition are known) the further conclusion may properly be drawn, namely, that the dominating rôle of diet in the prevention and causation of pellagra must be referred primarily to the character of the protein supply.

The distinctive clinical physiognomy of the disease precludes the assumption of any but a specific etiology; it must be assumed, therefore, that the essential etiological dietary factor is a specific defect in the protein mixture or, since protein is but a complex of amino-acids, different for different proteins, that it is a specific defect in the amino-acid supply either in the nature of an improper balance or more probably of a deficiency of some one or of some combination or combinations of amino-acids. This does not mean and we do not wish to be understood as suggesting that the diet associated with the production of pellagra is always complete with respect to all but the specific amino-acid factor. On the contrary, there is reason to believe that such diets may, and probably frequently, have other more or less serious shortcomings which may operate as accessory etiological factors and thus perhaps account for some of the "Protean" clinical manifestations of the disease.

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[1] In computing the caloric value the factor 4 was applied to protein and carbohydrate, and the factor 9 to fat. This therefore represents the available, not the gross, energy.

In 1918 Goldberger and Wheeler (43) gave expression to the opinion that as conventionally defined pellagra not improbably includes at least two commonly associated but etiologically distinct though fundamentally closely related syndromes, namely, (1) the syndrome comprehended by the phrase "pellagra sine pellagra," and (2) the dermal complex or pellagra without or with only slight subjective manifestations. While according to this idea, both syndromes are dependent primarily on a faulty diet, the first is to be regarded as the expression of a nutritive or metabolic failure, not in all respects peculiar to pellagra, whereas the second is to be considered as a reaction to a toxic substance or substances of a fairly specific type. Furthermore the initial appearance of the eruption on the genitalia in each of the cases with eruption occurring in their feeding experiment in convicts (21) suggested to Goldberger and Wheeler that the initial site of the eruption must be looked upon as a specific reaction, direct or indirect, to some special factor or combination of factors in the diet.

Our experience at this asylum lends support to the distinctions suggested by Goldberger and Wheeler. We have seen cases in female inmates in which, clinically, there was appreciable nothing but a well-marked dermatitis. Indeed, in one such instance there was, during the period immediately preceding the appearance of the erythema, a slight but steady gain in weight. Our observations here have also strongly impressed us with the idea that there is, as Goldberger and Wheeler suggest, some correlation between the type of diet and the site of the initial localization of the eruption.

It is of interest to note that this differentiation into a constitutional and a dermal type gains some support also from the study of the metabolism by Sullivan, Stanton, and Dawson (67), who found greater abnormality in the urinary findings in the systemic than in the dermal type of the disease.

With these considerations in mind we would suggest that with the conception of a specific amino-acid deficiency as the primary etiological factor should be coupled the idea that the character of the deficiency (the precise amino-acid combination) may vary within certain, probably narrow, limits. Hence it would seem permissible to conclude that the deficiency etiologically related to pellagra is probably some special combination or, within narrow limits, special combinations of amino-acids.

In this connection it should be pointed out that the possibility that some as yet unknown dietary essential, either alone or in combination with the protein factor, plays the dominating rôle in this disease, while perhaps very remote, is not excluded, and should, therefore, not be wholly disregarded.

In closing this section we should perhaps make clear that in dealing with the etiology of the disease we have intentionally centered our attention on those extrinsic factors which we believe to be essential to the production of the disease in the average normal individual. In doing so we have not been unmindful of the possibility that other, both extrinsic and intrinsic, factors may operate either to accelerate or to retard the development of the disease or of some of its distinctive manifestations. We have confined ourselves to a consideration of primary essential factors in the belief that progress in unraveling the complex problem of etiology could best be made by determining the fundamental essentials before dealing with accessory factors, however important these may be in certain individuals or special groups.

DISCUSSION.

It is of interest to note at the outset that the conclusion suggested by the observations herein reported, namely, that the primary etiological factor in pellagra is a specific defect in the amino-acid supply, probably of the nature of a deficiency, is in harmony with the other previously reported results of the series of studies of which the present is a part. These had in succession permitted the exclusion of one known vitamine after the other as an essential etiological factor (44); but not until the present observations were made did it seem permissible to exclude not only each of them individually but all of them together and with them, also, the mineral element as essential factors.

Most, if not all of the older dietary theories (zeist and antizeist), some of them seemingly very discordant, can, we believe, be harmonized on the basis of an amino-acid deficiency.

Of the newer viewpoints, that first suggested by Funk gains no support from our work; although, as we have already indicated, it is quite possible that a low or inadequate intake of any or all of the known vitamines or other food factors may play a more or less important accessory rôle.

On the surface there may seem to be a lack of harmony in our results with those of Voegtlin, Neil, and Hunter (34), who, as we noted in reviewing the literature, report observing very favorable therapeutic results following the administration of liver and thymus extracts containing both the antineuritic and the fat-soluble vitamine. Since these extracts are also reported to have contained unidentified amino-acids, the possibility is present that the beneficial effects noted are primarily attributable to these protein-building stones rather than to the contained vitamines. It should perhaps be recalled that these workers themselves did not attribute the favorable effects exclusively to the vitamines.

Our conclusions are in substantial agreement with those reached by Wilson. However, his use of Thomas's figures to appraise the biological value of a protein mixture, although in general, perhaps, very useful, seems to us to have the serious drawback, so far as pellagra is concerned, that a low biological protein value (so appraised) is not, in our view, necessarily indicative of a pellagra-producing defect. Since, as has already been pointed out, it must be assumed that the fault in the amino-acid complex related to pellagra is a specific one, it follows that individuals may conceivably subsist on diets faulty with respect to the protein mixture in other than this specific respect and not develop pellagra. Thus a pellagra-producing protein mixture may, according to Wilson's method of appraisal, always be of low biological value; but a protein of low biological value, so determined, may, we believe, not only not be pellagra-producing but actually be pellagra-preventing, so far, at least, as the distinctive dermatitis is concerned.

We think it important to keep this distinction in mind. It will aid in minimizing some of the perplexity and confusion of thought evidenced from time to time in discussions of the etiology of the disease. It may help to explain why the people of the Central Powers, during the war and since, though living on presumably faulty, perhaps, starvation diets, and suffering severely from malnutrition, have remained practically free from pellagra.

Some of the perplexity and confusion will also be prevented if it is not forgotten that the biological quality of a protein and its adequacy in relation to pellagra may, and doubtless frequently do, depend on the plane of intake. In our experience, a supplement of not over 40 grams of milk or beef proteins will, for practically all normal individuals, adequately supplement a pellagra-producing mixture of proteins from maize, wheat, rice, and cowpeas, but 20 grams (representing somewhat over a pint of milk or a quarter of a pound of round steak) may not do so. Thus it does not suffice merely to include milk or meat in a diet to prevent pellagra; the quantity of either of these or of other like foods alone or as supplements must be considerable to be effective. This may help to explain some of the instances of pellagra in individuals (including some of those very rare ones in nursing infants) who are alleged to have had a "good" diet. They did not consume enough for their particular needs.

It is readily understandable that the necessary minimum of a protein or mixture of proteins will, so far as pellagra is concerned (other things being equal), depend on its amino-acid make up. Unfortunately our knowledge of the latter is so meager that judgment must, for the present, be very tentative. Wilson (39), judging by the biological value of the protein as appraised on the basis of Thomas's figures—the amount available for assimilation, not the gross amount, being considered—suggests 40 as the minimum safe value for this factor. On the basis of practical experience, Goldberger (68) has tentatively suggested that for preventive purposes the diet should include a minimum of approximately 40 grams of animal protein (milk, cheese, meat, eggs) per day. This is a higher figure than Wilson's (if estimated by his method) and is higher than is needed by the average normal individual, but is not, we believe, too high when all types of individuals are considered.

For the purposes of treatment, the primary lesson to be drawn from this study is the need for emphasis on the protein factor. From the time of Casal, clinicians have repeatedly emphasized the importance of a "nutritious" diet, particularly one rich in animal foods, in the treatment of the disease. But notwithstanding Roussel's emphatic affirmation over half a century ago, that without diet all remedies fail, the full significance of a proper diet as the specific treatment is but just coming to be realized. Prevailing opinion, at least up to within three or four years ago, was probably accurately expressed by Dyer (49) when he said: "We are emphatic in the belief that most cases of pellagra will get well under medication, irrespective of diet." In consequence, medicinal specifics were sought for, and arsenic, atoxyl, arsphenamine, quinine hydrobromate, etc., were, from time to time, proposed as having virtues but little short of those of a specific remedy. Nor could the full significance of diet be justly appreciated until Goldberger, Waring, and Willetts, in 1915, for the first time convincingly showed that pellagra was completely preventable by diet without intervention of any other factor, hygienic or sanitary. This demonstration went far toward proving that diet is the primary controlling factor in the prevention and causation of the disease and thus pointed towards a proper diet as containing within itself the specific remedy for the disease.

With the search for the primary etiological factor narrowed down to a faulty amino-acid supply, we may expect, when the precise amino-acid defect is finally determined, that the specific remedy for the disease will at the same time have been found.

With this double end in view, we have made some tentative therapeutic tests with certain amino acids. These tests have not as yet been extensive enough to warrant any conclusions. We may say, however, that in two cases the dermal lesions seemed to show a markedly favorable response to cystine, and in a third the administration of a daily dose of one gram of cystine and two grams of tryptophane during a period of 31 days (the diet remaining unaltered), was accompanied by a weekly gain in weight and a slight improvement in diarrhea.

We hope to continue this line of study; but it seems wise to report these preliminary results, such as they are, in the hope that clinicians may be led to try cystine and tryptophane in the treatment of suitable cases, and thus aid in the determination of their value therapeutically and of their significance etiologically.

Summary.

The more important part of the evidence proving diet to be the primary controlling factor in the prevention and causation of pellagra is briefly summarized.

Cases of pellagra are reported that were observed to occur in individuals who were known to have consumed daily, during period of not less than two and one-half months immediately before the onset of the distinctive eruption, what is judged to have been a liberal supply of mineral elements and the known vitamines, which would indicate that a deficiency of these dietary factors is not essential in the causation of the disease.

These factors having thus been excluded, the dominating rôle of diet in the prevention and causation of pellagra must be referred primarily to the character of the protein (amino-acid) supply, this being the only other dietary factor at present known to be necessary to physiological well-being.

On the assumption that all the dietary factors essential in human nutrition are known, it may be concluded that the essential etiological dietary factor is a specific defect in the amino-acid supply, probably in the nature of a deficiency of some special combination or combinations of amino acids.

There is reason to believe that besides the specific amino-acid defect, pellagra-producing diets may and probably frequently have other more or less serious faults, including nonspecific amino-acid deficiencies which may operate as accessory etiological factors.

In some preliminary therapeutic trials with amino-acids the dermal lesions in each of two cases seemed to show a markedly favorable reaction to cystine; and in a third case a steady gain in weight, with some improvement in diarrhea, accompanied the administration of both cystine and tryptophane.

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SMALLPOX OUTBREAK AT POTEAU, OKLA.

The following account of an outbreak of smallpox at Poteau, Okla., is furnished by an officer of the Public Health Service who cooperated with officers of the State board of health in combating the spread of the disease at that place.

On December 5, 1921, a prisoner in the county jail at Poteau was taken sick. The man had been in Kansas City, Mo., from November 16–27, during which time an epidemic of smallpox of the virulent type was present in that city. On December 6 the prisoner expressed his belief that he "was getting smallpox," when he was visited by the jail physician. On December 9 the eruption appeared. The disease was of the discrete type, with a few confluent patches. The patient recovered. He had been successfully vaccinated 44 years previously.

The above case was reported to the city health officer December 18, and some quarantine measures were taken. In the meantime the patient had been in contact with about 30 other prisoners and with the county officers. On December 19 some of the other prisoners who desired it were vaccinated. From December 21, 1921, to January 5, 1922, 18 secondary cases appeared among the prisoners. Nine of these died during the period January 3–13, inclusive. Every prisoner in the jail who had not been vaccinated contracted the disease. Ten prisoners who had been successfully vaccinated within the three preceding years (while in the Army) did not contract the disease, although they were in intimate contact with virulent cases.